Description

Method for detection of acute generalized inflammatory conditions (SIRS), sepsis, sepsis-like conditions and systemic infections

The present invention relates to a method for in vitro detection of acute generalized inflammatory conditions (SIRS) according to claim 1 or claim 30, as well as the use of recombinantly or synthetically prepared nucleic acid sequences or peptide sequences according to claim 57 derived therefrom.

The present invention relates to a method for in vitro detection of acute generalized inflammatory conditions (SIRS) according to claim 2 or claim 31, as well as the use of recombinantly or synthetically prepared nucleic acid sequences or peptide sequences according to claim 58 derived therefrom.

The present invention relates to a method for in vitro detection of severe sepsis according to claim 3 or claim 32, as well as the use of recombinantly or synthetically produced nucleic acid sequences or peptide sequences according to claim 59 derived therefrom.

Part of the description of the present invention is a sequence listing of 1430 pages, consisting of three parts, i.e. part I to part III. Part I of the sequence listing comprises the SEQUENCE IDs: I.1 to I.6242, part II comprises the SEQUENCE IDs II.1 to II.130 and part III comprises the SEQUENCE IDs III.1 to III.4168.

The complete sequence listing with the parts I to III is part of the description and, thus, part of the disclosure of the present invention.

The present invention particularly refers to labels for gene activity for the diagnosis and for the optimization of the therapy of acute generalized inflammatory conditions (Systemic Inflammatory Response Syndrome (SIRS)). Additionally, the present invention relates to methods for detecting acute generalized inflammatory conditions and/or sepsis, sepsis-like conditions, severe sepsis and systemic infections as well as for a corresponding improvement of therapy of acute generalized inflammatory conditions (SIRS).

Further, for patients suffering from acute generalized inflammatory conditions (SIRS) the present invention relates to new possibilities of diagnosis that are obtained from experimentally proofed findings in connection with the occurrence of changes in gene activity (transcription and subsequent protein expression).

In spite of the fact that there have been improvements of the pathophysiologic understanding and the supportive treatment of patients in intensive care units, SIRS is a disease that occurs very frequently and contributes considerably to mortality in patients in intensive care units [2-5].

The criteria of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (ACCP/SCCM) of 1992 are the ones that became most accepted in the international literature as definition of the term SIRS [4]. According to this definition, SIRS (in this patent described as acute generalized inflammatory conditions) is defined as systemic response of the inflammatory system triggered by a noninfectious stimulus. At least two of the following criteria have to be fulfilled in this context: Fever >38°C or hypothermia <36°C, leukocytosis >12G/l or leukopenia <4G/l or shift to the left in the haemogram, heart rate >90/min, tachypnoea >20 breaths/min or PaCO2 <4.3 kPa, respectively.

The mortality rate in SIRS amounts to about 20 % and increases with the development of more severe organ dysfunctions [6]. The contribution of SIRS to morbidity and lethality is of multidisciplinary interest, as it increasingly puts the success of the most advanced or experimental treatment methods of many medicinal fields (e.g. cardiosurgery, traumatology, transplantation medicine, heamatology/onkology) at a risk, as they all are threatened by an increased risk of the development of an acute generalized inflammatory conditions. Thus, the decrease of morbidity and lethality of many seriously ill patients goes along with the improvement of prevention, treatment and particularly detection and observation of the progress of acute generalized inflammatory conditions.

SIRS is a result of complex and very heterogeneous molecular processes that are characterized by the incorporation of many components and their interactions on every organizational level of the human body: genes, cells, tissues, organs. The complexity of the underlying biological and immunological processes resulted in many kinds of studies comprising a wide range of clinical aspects. One of the results from these studies was that the evaluation of new therapies is rendered more difficult

due to the presently used critera which are quite unspecific and clinical based and which do not sufficiently show the molecular mechanisms [7].

Unfortunately, sepsis and consecutive organ dysfunctions still rank among the principal causes of death in non-cardiologic intensive care units [1-3]. It is supposed that 400,000 patients suffer from sepsis in the USA each year [4]. Lethality is about 40% and increases to 70-80% if a shock develops [5, 6]. The excess lethality independent from the underlying disease of the patient and the underlying infection amounts to 35% [8].

The criteria of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (ACCP/SCCM) of 1992 are the ones that became most accepted in the international literature as definition of the term sepsis [4]. According to these criteria [4] the grades of severity „systemic inflammatory response syndrom" (SIRS), „sepsis", „severe sepsis" and „septic shock" are clinically defined. According to this definition, SIRS (in this patent described as acute generalized inflammatory conditions) is defined as the systemic response of the inflammatory system triggered by a noninfectious stimulus. At least two of the following criteria have to be fulfilled in this context: Fever >38°C or hypothermia <36°C, leukocytosis >12G/l or leukopenia <4G/l or shift to the left in the haemogram, heart rate >90/min, tachypnoea >20 breaths/min or PaCO2 <4.3 kPa, respectively. According to the definition, sepsis are those clinical conditions in which the criteria of SIRS are fulfilled and an infection is detected as cause or it is at least very likely that it is the cause. A severe sepsis is characterized by the additional occurrence of organ dysfunctions. Frequent organ dysfunctions are changes in the state of consciousness, oliguria, lactate acidosis or sepsis-induced hypotension with a systolic blood pressure lower than 90 mmHg, or a pressure decrease of more than 40 mmHg of the initial value, respectively. If such a hypotension cannot be treated by administration of crystalloids and/or colloids and the patient further needs treatment with catecholamines, this is called a septic shock. Such a septic shock is detected in about 20% of all sepsis patients.

Whether and how catecholamines are administered during the treatment of patients suffering from severe sepsis depends on the physician. If the blood pressure decreases, many physicians react by administering large quantities of infusion solutions and, thus, avoid administering catecholamines, however, there are also many physicians who refuse this kind of proceeding and who administer catecholamines much earlier and at a higher dose, if the patient shows the same

clinical severity. The consequence is that in everyday practice patients suffering from the same clinical severity can be rated as belonging to the group „severe sepsis" or to the group "septic shock" [4] due to subjective reasons. This is why it became common in international literature to pool patients with the severity grades "severe sepsis" and "septic shock" [4] in one group. This is why the term "severe sepsis" used in this description is used according to the above mentioned consensus conference for patients with sepsis and additional proof of organ dysfunctions and, thus, comprises all patients of the groups "severe sepsis" and "septic shock" according to [4].

The mortality rate in sepsis amounts to about 40 % and increases to 70-80%, if a severe sepsis develops [5, 6]. The contribution of sepsis and severe sepsis to morbidity and lethality is of multidisciplinary interest. By comparison, the number of cases rose continuously (by 139% from 73.6 to 176 cases per 100,000 hospital patients from 1970 and 1977, for example) [7]. This increasingly puts the success of the most advanced or experimental treatment methods of many medicinal fields (e.g. viscercal surgery, transplantation medicine, heamatology/onkology) at a risk, as they all are threatened by an increased risk of the development of acute generalized inflammatory conditions. Thus, the decrease of morbidity and lethality of many seriously ill patients goes along with a progress in prevention and treatment and especially detection and observation of the progress of the sepsis and severe sepsis. This is why well-known authors have been criticizing for a long time that too much energy and financial resources have been spend on the search for therapeutics for sepsis in the past decade, instead of using them for improving sepsis diagnosis.

Sepsis is a result of complex and highly heterogeneous molecular processes that are characterized by the incorporation of many components and their interactions on every organizational level of the human body: genes, cells, tissues, organs. The complexity of the underlying biological and immunological processes resulted in many kinds of studies comprising a wide range of clinical aspects. One of the results from these studies was that the evaluation of new sepsis therapies is rendered more difficult due to the unspecific clinically based inclusioncriteria, which does not sufficiently show the molecular mechanisms [9].

These facts have created need for innovative diagnostic means that are supposed to improve the capability of the person skilled in the art to diagnose patients suffering from SIRS, sepsis, sepsis-like conditions, severe sepsis and systemic infection at an early stage, to render the severity of a SIRS measurable on a molecular basis and to

make it comparable in the clinical progress and to derive information concerning the individual prognosis and the reaction on specific treatments.

The contribution of sepsis with regard to morbidity and lethality is of multidisciplinary interest. Lethality of sepsis changed only marginally within the last decades, whereas, in comparison, the indices increased continuously (e.g. from 1979 to 1987 by 139 % from 73.6 to 176 per 100,000 in-patients) [7]. This increasingly puts the success of treatment of the most advanced or experimental therapy methods of various special fields (visceral surgery, transplantation medicine, heamatology/onkology) at a risk due to the fact that they all imply without exception an increase of the risk of sepsis. Thus, the decrease of morbidity and lethality of many seriously ill patients goes along with a progress in prevention and treatment and especially diagnosis of sepsis.

Sepsis is a result highly heterogeneous molecular processes that are characterized by the incorporation of many components and their interactions on every organizational level of the human body: genes, cells, tissues, organs. The complexity of the underlying biological and immunological processes resulted in many kinds of studies comprising a wide range of clinical aspects. One of the results from these studies was that the evaluation of new sepsis therapies is rendered more difficult due to relatively unspecific clinically-based inclusioncriteria which do not sufficiently show the molecular mechanisms [9].

Technological improvements, especially the development of microarray technology, are now rendering it possible for the person skilled in the art to compare 10 000 genes or more and their gene products at the same time. The use of such microarray technologies can now give hints on the conditions of health, regulation mechanisms, biochemical interactions and signalization networks. As the comprehension how an organism reacts to infections is improved this way, this should facilitate the development of enhanced modalities of detection, diagnosis and therapy of systemic disorders.

Microarrays have their origin in „southern blotting" [10], the first approach to immobilize DNA-molecules so that it can be addressed three-dimensionally on a solid matrix. The first microarrays consisted of DNA-fragments, frequently with unknown sequence, and were applied dotwise onto a porous membrane (normally nylon). It was routine to use cDNA, genomic DNA or plasmid libraries, and to mark the hybridized material with a radioactive group [11-13].

Recently, the use of glass as substrate and fluorescence for detection together with the development of new technologies for the synthesis and for the application of nucleic acids in very high densities allowed the miniaturizing of the nucleic acid arrays. At the same time, the experimental throughput and the information content were increased [14-16].

Further, it is known from WO 03/002763 that microarrays basically can be used for the diagnosis of sepsis and sepsis-like conditions.

The first explanation for the applicability of microarray technology was obtained through clinical studies on the field of cancer research. Here, expression profiles proofed to be valuable with regard to identification of activities of individual genes or groups of genes, correlating with certain clinical phenotypes [17]. Many samples of individuals with or without leukemia or diffuse lymphoma of large B-cells were analyzed and gene expression labels (RNA) were found and used for the classification of those kinds of cancer [17, 18]. Golub et al. found out that an individual gene is not enough to make reliable predictions, however, that predictions made on gene expression profiles of 53 genes (selected from more than 6000 genes that were present on the arrays) are highly accurate [17].

Alisadeh et al. [18] examined large B-cell lymphoma (DLBCL). The authors created expression profiles with a "lymph chip", a microarray bearing 18 000 clones of complementary DNA that was developed to monitor genes that are involved in normal and abnormal development of lymphocytes. By using cluster analysis, they managed to classify DILBCL in two categories that showed great differences with regard to the survival chance of patients. The gene expression profiles of these subtypes corresponded to two important stages of differentiation of B-cells.

To differentiate between symptoms that base on microbial infections and other symptoms of non-infectious etiology, which could indicate sepsis due to their **clinical** appearance, but are in fact not based on a systemic microbial infection, e.g. of symptoms that base on non-infectious inflammation of individual organs, the determination of gene expression profiles via differential diagnostics proofed to be particularly advantageous [19-22]. The use of body fluids for the measurement of gene expression profiles for the diagnosis of SIRS has not yet been described.

The point of origin of the invention disclosed in the present patent application is the realization that RNA levels different from normal values respectively peptide levels or peptide segment levels derivable from the RNA levels, that can be detected in a serum or plasma of a patient whose risk is high that he will be suffering from SIRS, or who suffers from symptoms that are typical for SIRS, can be detected before SIRS, sepsis, sepsis-like conditions, severe sepsis and systemic Infections are detected in biological samples.

Thus, it is an object of the present invention to provide a method for the detection, evaluation of the degree of severity, and/or the progress of the therapy, of SIRS and/or sepsis and/or severe sepsis and/or systemic infections.

This object is solved by a method with the characterizing features of the claims 1 to 3 and 30 to 32.

Further, it is an object of the present invention to provide a possible use of labels by means of the method according to claims 1 to 56.

This object is attained by the use according to claims 57 to 59.

The method of the invention is characterized in that the activity of one or more leading genes can be determined in a sample of a biological liquid of an individual. Additionally, SIRS and/or the success of a therapeutic treatment can be deduced from the presence and/or, if present, the amount of the determined gene product.

One embodiment of the present invention is characterized in that the method for in vitro detection of SIRS comprises the following steps:

a) Isolation of sample RNA from a sample of a mammal;
b) Labelling of the sample RNA and/or at least one DNA being a gene or gene fragment specific for SIRS, with a detectable label.
c) Contacting the sample RNA with the DNA under hybridization conditions;
d) Contacting control RNA representing a control for non-pathologic conditions, with at least one DNA, under hybridization conditions, whereby the DNA is a gene or gene fragment specific for SIRS;
e) Quantitative detection of the label signals of the hybridized sample RNA and control RNA;
f) Comparing the quantitative data of the label signals in order to determine whether the genes or gene fragments specific for SIRS are more expressed in the sample than in the control, or less.

One alternative embodiment of the present invention is characterized in that the method for in vitro detection of sepsis and/or sepsis-like conditions comprises the following steps:

g) Isolation of sample RNA from a sample of a mammal;

h) Labelling of the sample RNA and/or at least one DNA being a specific gene or gene fragment for sepsis and/or sepsis-like conditions, with a detectable label.

i) Contacting the sample RNA with the DNA under hybridization conditions;

j) Contacting sample RNA representing a control for non-pathologic conditions, with at least one DNA, under hybridization conditions, whereby the DNA is a gene or gene fragment specific for sepsis and/or sepsis-like conditions;

k) Quantitative detection of the label signals of the hybridized sample RNA and control RNA;

l) Comparing the quantitative data of the marking signals in order to determine whether the genes or gene fragments specific for sepsis and/or sepsis-like conditions are more expressed in the sample than in the control, or less.

One embodiment of the present invention is characterized in that the method for in vitro detection of severe sepsis comprises the following steps:

m) Isolation of sample RNA from a sample of a mammal;

n) Labelling of the sample RNA and/or at least one DNA being a specific gene or gene fragment for severe sepsis, with a detectable label.

o) Contacting the sample RNA with the DNA under hybridization conditions;

p) Contacting sample RNA representing a control for non-pathologic conditions, with at least one DNA, under hybridization conditions, whereby the DNA is a gene or gene fragment specific for severe sepsis;

q) Quantitative detection of the label signals of the hybridized sample RNA and control RNA;

r) Comparing the quantitative data of the label signals in order to determine whether the genes or gene fragments specific for severe sepsis are more expressed in the sample than in the control, or less.

A further embodiment of the present invention is characterized in that the control RNA is hybridized with the DNA before the measurement of the sample RNA and the label signals of the control RNA/DNA complex is gathered and, if necessary, recorded in form of a calibration curve or table.

Another embodiment of the present invention is characterized in that mRNA is used as sample RNA.

Another embodiment of the present invention is characterized in that the DNA is arranged, particularly immobilized, on predetermined areas on a carrier in form of a microarray.

Another embodiment of the invention is characterized in that the method is used for early detection by means of differential diagnostics, for control of the therapeutic progress, for risk evaluation for patients as well as for post mortem diagnosis of SIRS and/or sepsis and/or severe sepsis and/or systemic infections and/or septic conditions and/or infections.

Another embodiment of the present invention is characterized in that the sample is selected from: body fluids, in particular blood, liquor, urine, ascitic fluid, seminal fluid, saliva, puncture fluid, cell content, or a mixture thereof.

Another embodiment of the present invention is characterized in that cell samples are subjected a lytic treatment, if necessary, in order to free their cell contents.

Another embodiment of the present invention is characterized in that the mammal is a human.

Another embodiment of the invention is characterized in that the gene or gene segment specific for SIRS is selected from the group consisting of SEQUENCE ID

No. III.1 to SEQUECE ID No. III.4168, as well as from gene fragments thereof having at least 5-2000, preferably 20-200, more preferably 20-80 nucleotides.

Another embodiment of the invention is characterized in that the gene or gene segment specific for sepsis and/or sepsis-like conditions is selected from the group consisting of SEQUENCE ID No. I.1 to SEQUECE ID No. I.6242, as well as gene fragments thereof with 5-2000 or more, preferably 20-200, more preferably 20-80 nucleotides.

Another embodiment of the invention is characterized in that the gene or gene segment specific for severe sepsis is selected from the group consisting of SEQUENCE ID No. II.1 to SEQUECE ID No. II.130, as well as gene fragments thereof with 5-2000 or more, preferably 20-200, more preferably 20-80 nucleotides.

Another embodiment of the present invention is characterized in that the immobilized probes are labelled. As probes for this embodiment serve self-complementary oligonucleotides, so called molecular beacons. They bear a fluorophore/quencher pair at their ends, so that they are present in a folded hairpin structure and only deliver a fluorescence signal with corresponding sample sequence. The hairpin structure of the molecular beacons is stable until the sample hybridizes at the specific catcher sequence, this leading to a change in conformation and, thus, to the release of reporter fluorescence.

Another embodiment of the present invention is characterized in that at least 2 to 100 different cDNAs are used.

Another embodiment of the present invention is characterized in that at least 200 different cDNAs are used.

Another embodiment of the present invention is characterized in that at least 200 to 500 different cDNAs are used.

Another embodiment of the present invention is characterized in that at least 500 to 1000 different cDNAs are used.

Another embodiment of the present invention is characterized in that at least 1000 to 2000 different cDNAs are used.

Another embodiment of the present invention is characterized in that the cDNA of the genes listed in claim 10 is replaced by synthetic analoga as well as peptidonucleic acids.

Another embodiment of the present invention is characterized in that the synthetic analoga of the genes comprise 5-100, in particular about 70 base pairs.

Another embodiment of the present invention is characterized in that a radioactive label is used as detectable label, in particular ^{32}P, ^{14}C, ^{125}I, ^{155}Ep, ^{33}P or ^{3}H.

Another embodiment of the present invention is characterized in that a non-radioactive label is used as detectable label, in particular a color- or fluorescence label, an enzyme label or immune label, and/or quantum dots or an electrically measurable signal, in particular the change in potential, and/or conductivity and/or capacity during hybridizations.

Another embodiment of the present invention is characterized in that the sample RNA and control RNA bear the same label.

Another embodiment of the present invention is characterized in that the sample RNA and control RNA bear different labels.

Another embodiment of the present invention is characterized in that the cDNA probes are immobilized on glass or plastics.

Another embodiment of the present invention is characterized in that the individual cDNA molecules are immobilized onto the carrier material by means of a covalent binding.

Another embodiment of the present invention is characterized in that the individual cDNA molecules are immobilized onto the carrier material by means of adsorption, in particular by means of electrostatic and/or dipole-dipole and/or hydrophobic interactions and/or hydrogen bridges.

Another embodiment of the method according to the present invention for in vitro detection of SIRS is characterized in that it comprises the following steps:

a) Isolation of sample peptides from a sample of a mammal;
b) Labelling of the sample peptides with a detectable label;

c) Contacting the labelled sample peptides with at least one antibody or its binding fragment, whereby the antibody binds a peptide or peptide fragment specific for SIRS;

d) Contacting the labelled control peptides originating from healthy subjects, with at least one antibody or its binding fragment immobilized in form of a microarray on a carrier, whereby the antibody binds a peptide or peptide fragment specific for SIRS;

e) Quantitative detection of the label signals of the sample peptides and the control peptides;

f) Comparing the quantitative data of the label signals in order to determine whether the genes or gene fragments specific for SIRS are more expressed in the sample than in the control, or less.

Another alternative embodiment of the method according to the present invention for in vitro detection of sepsis and/or sepsis-like conditions is characterized in comprising the following steps:

g) Isolation of sample peptides from a sample of a mammal;

h) Labelling of the sample peptides with a detectable label;

i) Contacting the labelled sample peptides with at least one antibody or its binding fragment, whereby the antibody binds a peptide or peptide fragment specific for sepsis and/or sepsis-like conditions;

j) Contacting the labelled control peptides originating from healthy subjects, with at least one antibody or its binding fragment immobilized on a carrier in form of a microarray, whereby the antibody binds a peptide or peptide fragment specific for sepsis and/or sepsis-like conditions;

k) Quantitative detection of the label signals of the sample peptides and the control peptides;

l) Comparing the quantitative data of the label signals in order to determine whether the genes or gene fragments specific for sepsis and/or sepsis-like conditions are more expressed in the sample than in the control, or less.

Another embodiment of the method according to the present invention for in vitro detection of severe sepsis is characterized in comprising the following steps:

m) Isolation of sample peptides from a sample of a mammal;

n) Labelling of the sample peptides with a detectable label;

o) Contacting the labelled sample peptides with at least one antibody or its binding fragment, whereby the antibody binds a peptide or peptide fragment specific for severe sepsis;

p) Contacting the labelled control peptides stemming from healthy subjects, with at least one antibody or its binding fragment immobilized on a carrier in form of a microarray, whereby the antibody binds a peptide or peptide fragment specific for severe sepsis;

q) Quantitative detection of the label signals of the sample peptides and the control peptides;

r) Comparing the quantitative data of the label signals in order to determine whether the genes or gene fragments specific for severe sepsis are more expressed in the sample than in the control, or less.

Another embodiment of the present invention is characterized in that the antibody is immobilized on a carrier in form of a microarray.

Another embodiment of the present invention is characterized in providing an immunoassay.

Another embodiment of the invention is characterized in that the method is used for early detection by means of differential diagnostics, for control of the therapeutic progress, for risk evaluation for patients as well as for post mortem diagnosis of SIRS and/or sepsis and/or severe sepsis and/or systemic infections.

Another embodiment of the present invention is characterized in that the sample is selected from: body fluids, in particular blood, liquor, urine, ascitic fluid, seminal fluid, saliva, puncture fluid, cell content, or a mixture thereof.

Another embodiment of the present invention is characterized in that tissue- and cell samples are subjected to a lytic treatment, if necessary, in order to free the content of the cells.

Another embodiment of the present invention is characterized in that the mammal is a human.

Another embodiment of the invention is characterized in that the peptide specific for SIRS is an expression product of a gene or gene fragment selected from the group consisting of SEQUENCE ID No. III.1 to SEQUECE ID No. III.4168, as well as gene fragments thereof with 5-2000 or more, preferably 20-200, more preferably 20-80 nucleotides.

Another embodiment of the invention is characterized in that the peptide specific for sepsis and/or sepsis-like conditions is an expression product of a gene or gene fragment selected from the group consisting of SEQUENCE ID No. I.1 to SEQUENCE ID No. I.6242, as well as gene fragments thereof with 5-2000 nucleotides or more, preferably 20-200, more preferable 20-80 nucleotides.

Another embodiment of the invention is characterized in that the peptide specific for severe sepsis is an expression product of a gene or gene fragment selected from the group consisting of SEQUENCE ID No. II.1 to SEQUECE ID No. II.130, as well as gene fragments thereof with 5-2000 or more, preferably 20-200, more preferably 20-80 nucleotides.

Another embodiment of the present invention is characterized in that at least 2 to 100 different peptides are used.

Another embodiment of the present invention is characterized in that at least 200 different peptides are used.

Another embodiment of the present invention is characterized in that at least 200 to 500 different peptides are used.

Another embodiment of the present invention is characterized in that at least 500 to 1000 different peptides are used.

Another embodiment of the present invention is characterized in that at least 1000 to 2000 different peptides are used.

Another embodiment of the present invention is characterized in that a radioactive label is used as detectable label, in particular ^{32}P, ^{14}C, ^{125}I, ^{155}Ep, ^{33}P or ^{3}H.

Another embodiment of the present invention is characterized in that a non-radioactive label is used as detectable label, in particular a color- or fluorescence label, an enzyme label or immune label, and/or quantum dots or an electrically measurable signal, in particular the change in potential, and/or conductivity and/or capacity during hybridizations.

Another embodiment of the present invention is characterized in that the sample peptides and control peptides bear the same label.

Another embodiment of the present invention is characterized in that the sample peptides and control peptides bear different labels.

Another embodiment of the present invention is characterized in that the peptide probes are immobilized on glass or plastics.

Another embodiment of the present invention is characterized in that the individual peptide molecules are immobilized onto the carrier material by means of a covalent binding.

Another embodiment of the present invention is characterized in that the individual peptide molecules are immobilized on the carrier material by means of adsorption, in particular by means of electrostatic and/or dipole-dipole and/or hydrophobic interactions and/or hydrogen bridges.

Another embodiment of the present invention is characterized in that the individual peptide molecules are detected by means of monoclonal antibodies or their binding fragments.

Another embodiment of the present invention is characterized in that the determination of individual peptides by means of immunoassay or precipitation assay is carried out using monoclonal antibodies.

Another embodiment of the present invention is the use of recombinantly or synthetically produced nucleic acid sequences, partial sequences or protein-/peptide-sequences derived thereof, specific for SIRS, individually or as partial quantities as calibrator in SIRS-assays and/or to evaluate the effects and toxicity when screening for active agents and/or for the preparation of therapeutics as well as of substances and compounds that are designed to act as therapeutics, for prevention and treatment of SIRS.

Another embodiment of the present invention is the use of recombinantly or synthetically produced nucleic acid sequences, partial sequences or protein-/peptide-sequences derived thereof, specific for sepsis and/or sepsis-like conditions, individually or as partial quantities as calibrator in sepsis-assays and/or to evaluate the effects and toxicity when screening for active agents and/or for the preparation of therapeutics as well as of substances and compounds that are designed to act as therapeutics, for prevention and treatment of sepsis, sepsis-like systemic inflammatory conditions and sepsis-like systemic infections.

Another embodiment of the present invention is the use of recombinantly or synthetically produced nucleic acid sequences, partial sequences or protein-/peptide-sequences derived thereof, specific for severe sepsis, individually or as partial quantities as calibrator in sepsis-assays and/or to evaluate the effects and toxicity when screening for active agents and/or for the preparation of therapeutics as well as of substances and compounds that are designed to act as therapeutics, for prevention and treatment of severe sepsis.

It is obvious to the person skilled in the art that the individual features of the present invention shown in the claims can be combined with each other in any desired way.

The term leading genes as used in the present invention means all derived DNA-sequences, partial sequences and synthetic analoga (for example peptido-nucleic acids, PNA). In the present invention, it further means all proteins, peptides or partial sequences, respectively, or synthetic peptide mimetics decoded by leading genes are meant. The description of the invention referring to the determination of the gene expression is not a restriction but only an exemplary application of the present invention.

The description of the invention referring to blood is only an exemplary embodiment of the present invention. The term biological liquids as used in the present invention means all human body fluids.

One application of the method according to the invention is the measurement of differential gene expression with SIRS, sepsis, sepsis-like conditions, severe sepsis and systemic infections. For this measurement, the RNA is isolated from the whole blood of corresponding patients and a control sample of a healthy subject or of a subject that is not suffering from one of the above-mentioned disorders. Subsequently, the RNA is labelled, for example radioactively with ^{32}P or with dye molecules (fluorescence). All molecules and/or detection signals known in the state of the art for labelling molecules may be used as labelling molecules. The person skilled in the art is also aware of the corresponding molecules and/or methods.

The RNA thus labelled is subsequently hybridized with cDNA-molecules that are immobilized on a microarray. The cDNA-molecules immobilized on the microarray are a specific selection of genes according to claim 12 of the present invention for the measurement of SIRS, according to claim 13 for sepsis and sepsis-like conditions, according to claim 14 for severe sepsis and systemic infections.

The intensity signals of the hybridized molecules are measured afterwards by means of suitable instruments (phosporimager, microarray scanner) and analyzed by means of additional computer-based analysis. The expression ratios of the sample of the patient and the control are determined with the signal intensities measured. The expression ratios of the under- and/or overregulated genes indicate, as in the experiments described below, whether SIRS, sepsis, sepsis-like conditions, severe sepsis and systemic infections are present or not.

Another use of the method according to the invention is the measurement of the differential gene expression to determine how probable it is that the patient will respond to the planned therapy, and/or for determination of the reaction to a specialized therapy and/or the settlement of the end of the therapy in terms of a "drug monitoring" with patients suffering from SIRS, sepsis, sepsis-like conditions, severe sepsis and systemic infections. For this purpose, the RNA (sample RNA) is isolated from the blood samples of the patient, that have been taken in time intervals. The different RNA samples are labelled together with the control sample and hybridized with the selected genes that are immobilized on a microarray. Thus, the corresponding expression ratios show the probability that patients respond to the

planned therapy, and/or whether the started therapy is effective, and/or how long the patients' treatment has to go on, and/or whether the maximum effect of the therapy has already been achieved with the dose and duration applied.

Another use of the method according to the invention is the measurement of the binding grade of proteins, for example monoclonal antibodies, by means of the use of immunoassays, protein- and peptide arrays or precipitation assays. Durch die Bestimmung der Konzentration der von den Sequenzen der in Anwendungsbeispiel 1 aufgeführten Nukleinsäuren entsprechenden Proteine or Peptide kann auf ein erhöhtes Risiko zur Entwicklung einer SIRS geschlossen werden. Additionally, this procedure allows the differential diagnostic determination in patients suffering from SIRS, sepsis, sepsis-like conditions, severe sepsis and systemic infections.

Additionally, this indicates a higher risk of development of sepsis, sepsis-like conditions, severe sepsis and systemic infections.

Further advantages and features of the present invention will become apparent from the description of the embodiments as well as from the drawing.

It shows:

Figure 1 a 2-dimensional gel comprising a precipitated serum protein of a patient suffering from sepsis that is applied to it, and

Figure 2 a 2-dimensional gel comprising a precipitated serum protein of a control that is applied to it.

Embodiment 1 - SIRS:

Studies of differential gene expression with patients suffering from SIRS.

Whole blood samples of patients who were under the care of a surgical intensive care unit were examined for the measurement of the differential gene expression in connection with SIRS.

Control samples were whole blood samples of the patients that were drawn immediately before the operation. No one of these patients showed an infection

and/or clinical signs of SIRS (defined according to the SIRS-criteria [4]) at this point of time or before the stationary treatment.

Additionally, whole blood samples of the same patients who had been subjected to a surgery, were drawn four hours after the operation (patient samples). Each of these patients developed SIRS after the surgery. A range of characteristics of the patients suffering from SIRS are shown in table 1. In Table 1, data with regard to age, gender, diagnosis as well as duration of the extracorporeal treatment are given.

Table 1: Data of the group of patients

Patient	Gender	Age	Diagnosis	Duration of extracorporeal treatment [min]
1	male	57	coronary heart disease	82
2	male	70	coronary heart disease	83
3	female	67	coronary heart disease	72
4	male	70	coronary heart disease	55

After the whole blood had been drawn, the total RNA was isolated using the PAXGene Blood RNA Kit according to the producer's (Quiagen) instructions. Subsequently, the cDNA was synthesized from the total RNA by means of reverse transcriptions with Superscript II RT (Invitrogen) according to the producer's instructions, labelled with aminoallyl-dUTP and succinimidylester of the fluorescent dyes Cy3 and Cy5 (Amersham), and hydrolyzed.

The microarrays (Lab-Arraytor human 500-1 cDNA) of the company SIRS-Lab GmbH were used for the hybridization. These micorarrays are loaded with 340 humane cDNA-molecules. The 340 humane cDNA-molecules are 3-fold immobilized in three subarrays on each microarray.
The prepared and labelled samples were hybridized with the microarrays according to the producer's instructions and subsequently washed. The fluorescence signals of the hybridized molecules were measured by means of a scanner (AXON 4000B) .

Analysis

One test was analyzed by means of scanned pictures of the microarrays after hybridization. The mean intensity value of the detected spots was defined as the measured expression value of the corresponding gene. Spots were automatically

identified and their homogeneity was checked. The analysis was controlled manually. In addition to the desired information, namely the amount of nucleic acids bound, contain the detected signals also background signals which are caused by unspecific bindings to the surface of the membrane. The definition of the signals of the background rendered the optimum differentiation between spots and the surface of the chip possible, which also showed color effects. For the analysis of the microarrays blank spots were chosen as background. The mean expression value of the chosen blank spots within one block (of 14 times 14 spots) was subtracted from the expression values of the gene spots (in the corresponding block).

Point signals not caused by binding of nucleic acids but by dust particles or other disturbances on the filter, could be told from real spots because of their irregular shape and were excluded from further analysis.

In order to render the values between the 3 subarrays and between different microarrays comparable, it was necessary to normalize the data afterwards. Due to the high number of spots on the microarray, the mean value of all expression values was set as normalization reference. The mean expression per gene was calculated by choosing the two (from three) repetitions that were closest to each other.

The expression ratios of the samples of the control and the patients were calculated from the signal intensities using the software AIDA Array Evaluation. The criteria for the grading of the examined genes was the level of the expression ratio. The interesting genes were those which were most overexpressed or underexpressed, respectively, compared with the control samples.

Table 2 shows that 57 genes of the patient sample were found, which were significantly overexpressed, if compared with the control sample. Table 3 shows that 16 genes of the patient sample were found, which were significantly underexpressed, if compared with the control sample. Those results show that the genes listed in table 2 and table 3 correlate with the occurrence of SIRS. Thus, the gene activities of the genes mentioned are labels for a diagnosis of SIRS.

Table 2: Significantly increased transcription activities and their relative ratio to the control sample in SIRS

GenBank Accession-No.	Hugo-Name	Patient 1	Patient 2	Patient 3	Patient 4	SEQUENCE-ID
XM_051958	ALOX5	2.43	1.49	1.81	1.40	III.36

XM_015396	ALOX5AP	3.71	7.39	3.89	2.68	III.37
XM_008738	BCL2	1.16	6.76	1.55	1.04	III.38
BC016281	BCL2A1	13.71	10.29	1.41	4.36	III.96
NM_021073	BMP5	2.02	1.83	1.78	1.51	III.39
XM_002101	BMP8	2.32	10.85	1.31	0.87	III.40
XM_045933	CAMKK2	2.20	1.26	1.95	1.13	III.41
XM_055386	CASP1	1.40	1.76	1.89	1.45	III.42
NM_004347	CASP5	1.92	2.77	0.67	1.89	III.43
NM_004166	CCL14	1.24	1.58	2.46	0.77	III.91
XM_012649	SCYA7	1.24	9.78	0.85	1.82	III.93
NM_001760	CCND3	1.23	2.68	1.56	1.12	III.44
NM_000591	CD14	3.45	4.43	1.76	2.05	III.45
XM_038773	CD164	0.84	1.91	3.26	3.15	III.46
XM_048792	CD1A	3.24	3.10	1.00	1.11	III.47
NM_001779	CD58	2.14	2.11	1.54	2.91	III.48
XM_002948	CD80	1.69	1.16	2.25	0.69	III.51
XM_027978	CFLAR	2.33	4.97	1.44	1.39	III.52
NM_000760	CSF3R	1.55	1.47	1.81	1.02	III.53
XM_012717	CSNK1D	1.95	3.15	1.24	1.32	III.54
XM_048068	SCYD1	3.70	12.12	0.86	3.88	III.94
XM_051229	CXCR4	2.33	2.10	2.15	1.60	III.55
XM_039625	DUSP10	2.49	3.77	0.90	1.10	III.57
XM_010177	DUSP9	2.17	5.27	1.12	1.63	III.58
XM_055699	ENTPD1	1.91	3.18	0.71	0.86	III.59
XM_007189	FOXO1A	1.61	3.10	1.09	1.67	III.60
XM_012039	FUT4	1.55	5.07	1.88	0.93	III.61
XM_040683	HPRT1	5.15	66.19	1.44	2.28	III.62
NM_017526	OBRGRP	1.93	1.10	1.53	1.40	III.63
XM_049516	ICAM1	1.27	1.88	2.05	1.30	III.64
XM_049531	ICAM3	2.31	2.32	1.61	1.45	III.65
XM_041744	IER3	4.17	7.25	1.98	2.08	III.66
XM_048562	IFNAR1	2.16	4.87	1.09	2.36	III.67
XM_006447	IL10RA	1.02	1.51	1.96	0.67	III.68
M90391	IL-16	1.77	1.50	1.16	1.09	III.69
XM_002765	IL1R2	2.84	12.75	1.03	2.75	III.70
NM_000418	IL4R	3.34	6.44	2.05	2.79	III.71
XM_057491	IL6	1.72	1.48	1.53	1.37	III.72
NM_002184	IL6ST	2.50	9.25	1.07	1.87	III.73
NM_000634	IL8RA	2.27	3.73	1.45	1.68	III.74
NM_006084	ISGF3G	1.72	1.08	2.54	1.12	III.75
XM_045985	ITGA2B	3.69	2.00	0.83	3.79	III.76
XM_008432	ITGA3	2.11	7.62	1.08	1.06	III.77
XM_028642	ITGA5	2.49	4.48	1.39	3.54	III.78
XM_036107	ITGB2	1.72	1.13	2.08	1.13	III.79
XM_009064	JUNB	2.21	1.84	3.59	2.05	III.80
XM_036154	LAMP2	1.79	1.68	1.62	1.41	III.81

GenBank Accession-No.	Hugo-Name	Patient 1	Patient 2	Patient 3	Patient 4	SEQUENCE-ID
XM_042066	MAP3K1	2.06	7.67	2.91	8.93	III.82

NM_001315	MAPK14	2.50	12.01	0.90	4.20	III.83
NM_003684	MKNK1	2.58	17.17	1.74	1.83	III.84
U68162	MPL	2.58	1.10	1.39	6.99	III.85
NM_004555	NFATC3	1.40	1.70	2.80	0.75	III.86
XM_006931	OLR1	1.53	5.01	1.10	3.16	III.87
XM_039764	PDCD5	1.11	3.09	1.21	1.95	III.88
XM_029791	PIK3C2G	0.93	1.62	0.96	1.52	III.89
NM_006219	PIK3CB	1.52	0.99	0.94	1.66	III.95
XM_043864	PIK3R1	1.81	4.07	1.48	1.26	III.90

Table 3: Significantly reduced transcription activities and their relative ratio to the control sample in SIRS

GenBank Accession-No.	HUGO Name	Patient 1:	Patient 2:	Patient 3:	Patient 4:	SEQUENCE-ID
BC001374	CD151	0.00	0.00	0.39	0.71	III.3
XM_006454	CD3G	0.63	0.40	0.75	1.01	III.6
XM_043767	CD3Z	0.43	0.00	0.82	0.77	III.7
XM_056798	CD81	0.50	1.12	0.32	0.00	III.8
M26315	CD8A	1.45	0.00	0.30	1.31	III.9
NM_004931	CD8B1	0.40	0.90	0.50	1.19	III.10
NM_001511	CXCL1	0.09	0.00	0.50	1.34	III.13
XM_057158	ADCY6	1.17	0.00	0.42	1.34	III.11
XM_044428	ICAM2	0.00	1.16	0.50	1.10	III.14
NM_000880	IL7	0.00	1.06	0.74	0.10	III.16
L34657	PECAM-1	0.68	0.39	1.13	0.64	III.24
XM_044882	PTGS1	0.00	1.34	0.52	0.76	III.25
XM_035842	SCYA5	0.60	0.50	0.80	0.99	III.29
NM_021805	SIGIRR	0.00	0.40	0.45	0.66	III.30
XM_057372	TNFRSF5	0.00	0.49	0.59	1.03	III.34
NM_003809	TNFSF12	1.34	0.99	0.53	0.60	III.35

These characteristic changes can be used for the method according to the present invention according to claim 1 and 30, for example.

In the appended sequence listing of 1430 pages (sequence ID: III.1 to sequence ID: III.4168), which is part of the present invention, the gene bank accession numbers

indicated in tables 2 and 3 (access via internet via http://www.ncbi.nlm.nih.gov/) of the individual sequences are each allocated to one sequence ID.

Embodiment 2 - SIRS:

Study of the gene expression of three patients suffering from SIRS, and one control.

The gene expression of three patients suffering from SIRS and one control were measured. All patients developed SIRS as described in the criteria according to [4]. The control sample was taken from one patient who was subjected to surgical treatment, but who did not show any SIRS during this stationery treatment. The date of the patients suffering from SIRS and the control are summarized in table 4.

Table 4: Characteristics of the samples of patients and controls

Patient	Gender	Age	Diagnosis	Apache Score [point]	SAPS II [point]
1	male	50	coronary heart disease	18	36
2	male	70	caecum perforation	19	64
3	male	67	aortic valve insuffiency	9	21
Control	**Gender**	**Age**	**Diagnosis**	**Apache Score [point]**	**SAPS II [point]**
1	male	70	fracture of the skull cap	1	12

After the whole blood had been drawn, the total RNA was isolated using the RNAeasy-Kit according to the producer's (Quiagen) instructions. Subsequently, the cDNA was synthesized from the total RNA by means of reverse transcription with Superscript II RT (Invitrogen), labelled with ^{33}P according to the producer's instructions, and hydrolyzed.

For the hybridization membrane filters of the Deutschen Ressourcenzentrum für Genomforschung GmbH (a German center for genome research) (RZPD) were used. This membrane filter was loaded with about 70,000 human cDNA-molecules.

The prepared and labelled samples were hybridized with the membrane filter according to the RZPD's instructions and subsequently washed. The radioactive signals were analyzed after 24 hours of exposition in a phosphorimager.

Analysis

The analysis of the gene expression data from the radioactively labelled filters bases on the measurement of the dye intensities in the digitalized picture. This is achieved by the definition of circular areas over all 57600 spot positions, in which the pixel intensities are integrated. The areas are automatically positioned as accurately as possible over the spots by means of the analysis software (AIDA Array Evaluation, raytest Isotopenmessgeräte GmbH).

In addition to the desired information, namely the amount of nucleic acids bound, contain the detected signals also background signals which are caused by unspecific bindings to the surface of the membrane. In order to eliminate these influences, the background signals are determined in 4608 empty areas of the filter and subtracted as background noise from the hybridization signals.

In order to render the values of different filters comparable, it is necessary to normalize the data afterwards. Due to the high number of spots on the filter, the mean value of all expression values is set as normalization reference. Further, it is necessary to exclude minor spot signals (lower than 10% of the average expression signal), as these are subject to a percentually high error, and would lead to considerable variations of the results when used later on for calculations.

The selection of the genes relevant to SIRS bases on the comparison of the gene expression values in a control person not suffering from SIRS compared to the patient suffering from SIRS. The criteria for the grading of the examined genes is the level of the expression ratio. When comparing the genes of the patients with those of the control, the genes, that were significantly overexpressed or underexpressed, respectively, are the interesting ones.

Table 5 shows that there were 24 genes found in the patient sample, which were significantly overexpressed, if compared with the control sample. Table 6 shows that there were 24 genes found in the patient sample, which were significantly underexpressed, if compared with the control sample. Those results show that the genes listed in table 5 and table 6 correlate with the occurrence of SIRS. Thus, the genes mentioned are leading genes for the diagnosis of SIRS.

Table 5: Significantly increased transcription activities and their relative ratio to the control sample in SIRS

GenBank Accession No.	HUGO Name	Patient 1:	Patient 2:	Patient 3:	SEQUENCE-ID
R33626	TFAP2A	57.57	30.43	96.57	III.135
N54839	CRSP3	47.17	29.00	63.17	III.180
AA010908	LCAT	32.90	15.00	18.60	III.189
R59573	TU12B1	85.50	60.50	49.00	III.198
R65820	GEF	38.00	45.80	78.00	III.222
N30458	NCL	26.57	20.00	17.86	III.252
H86783	RINZF	43.33	17.00	31.33	III.274
R11676	CDC20	30.75	52.00	55.25	III.300
H79834	SLC20A2	16.56	14.33	27.44	III.309
H05746	SLC12A5	70.78	20.00	17.22	III.313
N21112	ARHGEF12	62.00	14.50	27.00	III.321
R71085	PCANAP7	23.00	17.63	21.96	III.325
R40287	NIN283	35.00	28.00	28.00	III.331
H52708	PDE2A	32.78	14.11	59.22	III.351
AF086381	GNPAT	18.94	19.75	25.63	III.353
W57892	FN1	23.61	14.67	17.06	III.381
H75516	KIN	19.23	17.15	20.00	III.389
R59212	MN1	19.65	16.65	18.61	III.404
H62284	CMAH	23.40	36.20	32.40	III.421
W16423	GCMB	23.83	45.67	21.00	III.446
N40557	U5	55.78	20.67	22.11	III.454
H52695	DDC	14.80	13.70	22.30	III.472
R68244	HMG14	15.81	23.19	27.56	III.493
R34679	ITGB8	19.20	32.00	79.20	III.502

Table 6: Significantly reduced transcription activities and their relative ratio to the control sample in SIRS

GenBank Accession No.	HUGO Name	Patient 1:	Patient 2:	Patient 3:	SEQUENCE-ID
H18595	RPL10A	0.03	0.07	0.15	III.181
N90220	DGUOK	0.04	0.07	0.12	III.202
R19651	H19	0.09	0.07	0.19	III.329
R52108	UBE2D2	0.13	0.07	0.02	III.369
R83836	LYN	0.07	0.03	0.18	III.387
H04648	CSF2RB	0.06	0.07	0.13	III.395
H27730	PPP2R1B	0.09	0.07	0.16	III.416
N70020	PRO2822	0.10	0.04	0.11	III.422
N52437	CHI3L2	0.07	0.08	0.16	III.440
W96179	GCLM	0.04	0.01	0.19	III.450
H42506	GABARAP	0.08	0.03	0.17	III.470
H66258	SCP2	0.10	0.05	0.21	III.474
N38985	RAP140	0.10	0.06	0.21	III.524
N73912	TMP21	0.09	0.07	0.08	III.533
N51024	TEGT	0.08	0.06	0.07	III.537
R99466	EEF1A1	0.07	0.02	0.14	III.636
R14080	CAMLG	0.11	0.02	0.18	III.662
W93782	XPC	0.12	0.05	0.21	III.664
N91584	RPS6	0.06	0.05	0.12	III.981
W52982	PIG7	0.05	0.07	0.10	III.1040
AA033725	KLF8	0.06	0.08	0.19	III.1163
N20406	SRP14	0.10	0.04	0.16	III.1193
T83104	TAF2F	0.02	0.05	0.12	III.1258
H79277	CASP8	0.12	0.06	0.13	III.1305

These characteristic changes can be used for the method according to the present invention according to claim 1 and 30, for example.

In the appended sequence listing of 1430 pages (sequence ID: III.1 to sequence ID: III.4168), which is part of the present invention, the gene bank accession numbers indicated in tables 5 and 6 (access via internet via http://www.ncbi.nlm.nih.gov/) of the individual sequences are each allocated to one sequence ID.

Embodiment 3 - Sepsis:

Study of the gene expression of one patient suffering from an early sepsis and one control sample.

The gene expression of one case of an early sepsis and one control sample were measured. The patient's data are summarized in table 7.

Table 7: Data of the samples of patients and controls

	Gender	Age [a]	Weight/Height	Main diagnosis	Intercurrent diagnosis	Operations	Indication	Apache Score [point]	
Patient	male	70	78 kg/178 cm	septic shock after caecum perforation and post operative anastomotic leak	intestine-, instable sternum	1. Anastomotic- and sigma re-resection, rectum dead end blockage 2. Punctation tracheotomy (Griggs) 3. re-wiring 4. subtotal hemiclolectomy right side 5. definitive ileostomy surgery	Sepsis/ septic shock	19	6
Control	male	35	90 kg/180 cm	Fracture of the skull, scalp haematoma	small hygroma on both sides	1. Craniotomy and definite haemostasis	Intracranial bleeding	1	1

After the whole blood had been drawn, the total RNA was isolated using RNAeasy according to the producer's (Quiagen) instructions. Subsequently, the cDNA was synthesized from the total RNA by means of reverse transcriptions with Superscript II RT (Invitrogen), labelled with ^{33}P, according to the producer's instructions, and hydrolyzed.

For the hybridization membrane filters of the Deutschen Ressourcenzentrum für Genomforschung GmbH (RZPD) were used. This membrane filter was loaded with about 70,000 humane cDNA-molecules.

The prepared and labelled samples were hybridized by means of the membrane filter according to the RZPD's instructions and subsequently washed. The radioactive signals were analyzed after 24 hours of exposition in a phosphorimager.

The expression ratios of the samples of the patients and the control were calculated from the signal intensities using the AIDA Array Evaluation software.

Table 8 shows that 230 genes of the patient sample were found, which were significantly overexpressed (expression ratios between 13.67 and 98.33), if compared with the control sample. Table 3 further shows that 206 genes of the patient sample were found, which were significantly underexpressed (expression ratios between 0.01 and 0.09), if compared with the control sample. Those results show that the genes listed in table 2 and table 3 correlate with the occurrence of SIRS. Thus, the genes mentioned are leading genes for the diagnosis of an early sepsis.

Table 8: Expression ratio of overexpressed genes of samples of patients and controls

GenBank Gene Bank Accession No.	HUGO Name	Expression ratio of overexpressed genes compared to control	SEQUENCE-ID
	FLJ20623	90.13	I.325
AI272878	FGF20	73.48	I.268
AI218453	FLJ22419	48.8	I.294
AI473374	SPAM1	42.63	I.235
AI301232	PRG4	36.79	I.262
AI452559	FLJ13710	32	I.240
AI339669	FLJ21458	31	I.248
AI142427	CGRP-RCP	30	I.331
AA505969	LOC56994	26.67	I.486
AI333774	AGM1	26.19	I.251
W86875	PSEN1	25.66	I.903
AI591043	NR2E3	25	I.196
AI128812	RBM9	23.56	I.324
AA453019	FLJ21924	23.07	I.672
AI690321	KCNK15	22.71	I.134
AA918208	ADAM5	21.83	I.363
AI344681	ABCA1	21.42	I.259
AI654100	KIAA0610	21.04	I.168
AI086719	FLJ12604	20.95	I.326
AA453038	LOC63928	20.74	I.671
AI740697	SP3	20.5	I.114
AI332438	KIAA1033	20.17	I.253
AI734941	MSR1	19.93	I.116
AA541644	PRV1	19.51	I.489
AA513806	C5ORF3	19.3	I.485
AI381513	B4GALT7	18.81	I.273
AI671360	SIM1	18.55	I.154
AI624830	SAGE	17.54	I.187
AI001846	KIAA0480	17.54	I.358
AA504336	TRAP95	17.25	I.495
AI142901	IMPACT	17.15	I.330
AI077481	SEMA5B	17.13	I.327
H41851	TNFRSF12	17.05	I.1511
AI160574	FLJ23231	17	I.314
AI033829	KIF13B	16.59	I.339
AI554655	HLALS	16.59	I.219
AI074113	LOC51095	16.4	I.328
AA992716	KIAA1377	16.14	I.348
AI382219	SETBP1	16.08	I.272
AI469528	KIAA1517	15.89	I.232
AI090008	NFYB	15.76	I.349
AI203498	WRN	15.72	I.310
AI832179	HPGD	15.66	I.65
AI278521	SPRR3	15.61	I.265
AA909201	FLJ23129	15.12	I.361

AI383932	ZNF214	14.98	I.269
AA455096	MDM1	14.9	I.652
AA953859	NOL4	14.68	I.363
GenBank Accession-No.	**Hugo Name**	Expression ratio of overexpressed genes compared to control	SEQUENCE-ID
R56800	GDF1	14.67	I.1755
AI676097	FCER1A	14.54	I.151
AI380703	KIAA1268	14.51	I.275
AI832086	RTKN	14.51	I.66
AI125328	FLJ22490	14.33	I.317
AI056693	LOC57115	14.3	I.329

Table 9: Expression ratio of underexpressed genes of samples of patients and controls

GenBank Accession No.	Hugo Name	Expression ratio of underexpressed genes compared to control	SEQUENCE-ID
R15296	C9ORF9	0.01	I.2050
AA609149	FLJ10058	0.01	I.375
AI566451	KAI1	0.01	I.211
AI334246	PDCD7	0.01	I.250
H38679	NXPH3	0.01	I.1477
AI696866	KIAA1430	0.01	I.130
AI922915	FLJ00012	0.01	I.23
AI889612	KPNA6	0.01	I.46
AI921695	FLJ23556	0.02	I.26
AA410933	HRH1	0.02	I.764
AA705423	LOC57799	0.02	I.383
AI206507	RAD54B	0.02	I.298
AI921327	MED6	0.02	I.28
AI682701	VNN1	0.02	I.146
H82822	METAP2	0.02	I.1352
AI890612	MAGE1	0.02	I.42
AI262169	ALDOB	0.02	I.257
H44908	C21ORF51	0.02	I.1502
AI572407	FLJ22833	0.02	I.203
AI924869	STX4A	0.02	I.19
AI925556	AF140225	0.02	I.12
AI798388	KIAA0912	0.03	I.95
AI623978	SCEL	0.03	I.188
AI889598	MLYCD	0.03	I.47
AI889648	PAWR	0.03	I.45
AI431323	AREG	0.03	I.237
AA446611	CDH6	0.03	I.706
AI697365	P53DINP1	0.03	I.129
H82767	VAMP3	0.03	I.1353
AI688916	FLJ10933	0.03	I.137
AI888660	FLJ11506	0.03	I.51
AI890314	RAB6B	0.03	I.43
AI653893	LAMA5	0.03	I.169
R89811	HGFAC	0.03	I.1462
AI863022	MAGEA4	0.04	I.59
AA749151	XPOT	0.04	I.378
AI355007	ITPKB	0.04	I.246
AI582909	MESDC2	0.04	I.201
AI832016	APOL1	0.04	I.67
H11827	THOP1	0.04	I.1597
AI560205	KIAA1841	0.04	I.216
AA503092	UMPH1	0.04	I.490
AI932616	FLJ22294	0.04	I.5
AI799137	FLJ11274	0.04	I.93
AI686838	SARDH	0.04	I.142

AI623132	SREC	0.04	I.189
GenBank Accession-No.	**HUGO-Name**	**Expression ratio of underexpressed genes compared to control**	**SEQUENCE-ID**
R96713	DKFZP434A0131	0.04	I.1442
AI674926	LBC	0.04	I.152
AI886302	HRI	0.04	I.53
AI434650	MGC2560	0.04	I.238
AI631380	GNG4	0.04	I.180
AA508868	ORC6L	0.04	I.491
AI620374	HP1-BP74	0.04	I.190
AI679115	KIAA1353	0.04	I.148
AA652703	MRPL49	0.04	I.386
AI355775	CDK3	0.04	I.245

These characteristic alterations can be used in particular for the method of the present invention according to claim 2 and/or 31.

In the appended sequence listing of 1430 pages (sequence ID: III.1 to sequence ID: III.4168), which is part of the present invention, the gene bank accession numbers (access via internet via http://www.ncbi.nlm.nih.gov/) indicated in tables 8 and 9 of the individual sequences are each allocated to one sequence ID.

Implementation:

Preparation of RNA. The conditioned media were removed from the culture flasks and the adherent cells were lysed directly in the culture flasks using TRIzol-reagent (GIBCO/BRL) according to the producer's instructions. One deproteinization cycle was carried out and afterwards, the RNA was precipitated by adding isopropyl alcohol, afterwards rinsed with ethyl alcohol, and again solved in 200 µl RNA-save resuspension solution (Ambion, Austin, TX). The RNA preparations were degraded with 0.1 units/µl DNase I, in DNase 1 buffer from CLONTECH. Additionally, proteins were removed from the RNA units in an alcohol mixture comprising phenol, chloroform and isoamyl alcohol, precipitated by adding ethyl alcohol, and solved in 50-100µl RNA-save resuspension solution. The RNA concentration was spectrophotometrically determined, provided that $1A_{260}$ corresponds to a concentration of 40 µg/ml. The samples were adapted to a final concentration of 1 mg/ml und stored at 80°C. No signs of deterioration of quality were observed. By means of agarose electrophoresis it was evaluated whether the RNA preparations were complete (i.e. they were not decayed into their components), here, RNA-standards (GIBCO/BRL)

were used. Each of the preparations described herein contained intact RNA the 28S-, 18S- and 5S-bands of which were clearly detectable (data not given). No recognizable differences between healthy and infectious cells were determined with regard to the electrophoretically determined RNA samples.

Preparation of radioactively labelled cDNA-samples and hybridzing by means of DNA arrays. The cDNA-synthesis was carried out according to the producer's instructions using gene specific primer (CLONTECH) and [^{32}P]-dATP with Moloney Murine Leukemea Virus Reverse Transkriptase (SuperScript II, GIBCO/BRL). For the cDNA-synthesis, the same amounts of RNA (5 µg) were used from each sample.

Alternative

RNA was extracted from the tissue samples by means of guanidinium thiocyanate and afterwards centrifuged in CsCl as described [19] . The RNA was extracted according to the producer's instructions from the cell lines with RNAzol (Biotex Laboratories, Houston). The poly(A) RNA was isolated from 500 µg RNA by means of DynaBeads (Dynal, Oslo), as described in the producer's recommendations.
The differences in the gene expression were examined using Atlas Array membranes (CLONTECH). A first short step was the transcription of 1 µg RNA of each cell line in [-^{32}P]dATP-labelled cDNA at a time.

Analysis

The analysis of the gene expression data from the radioactively labelled filters bases on the measurement of the dye intensities in the digitalized picture. This is achieved by the definition of circular areas over all 57600 spot positions, in which the pixel intensities are integrated. The areas are automatically positioned as accurately as possible over the spots by means of the analysis software (AIDA Array Evaluation, raytest Isotopenmessgeräte GmbH).

In addition to the desired information, namely the amount of nucleic acids bound, contain the detected signals also background signals which are caused by unspecific bindings to the surface of the membrane. In order to eliminate these influences, the background signals are determined in 4608 empty areas of the filters and subtracted as background noise from the hybridization signals.
It is possible to distinguish between punctual signals that are caused on the filter by dust particles or other disturbances instead of binding of nucleic acids, and real

spots, due to their irregular form, and the punctual signals are excepted from further analysis.

In order to render the values of different filters comparable, it was necessary to normalize the data afterwards. Due to the high number of spots on the filter, the mean value of all expression values is set as normalization reference. Further, it is necessary to exclude minor spot signals (lower than 10% of the average expression signal), as these are subject to a percentually high error, and would lead to considerable variations of the results when used later on for calculations.

The selection of the genes relevant to SIRS/sepsis bases on the comparison of the gene expression values in a control person without SIRS/sepsis compared to one patient at a time suffering from sepsis/SIRS. The criteria for the grading of the examined genes is the level of the expression ratio. The interesting genes are those which were most overexpressed or underexpressed, respectively, in the patients compared with the control.

Embodiment 4 - Sepsis:

Study of the protein expression of one patient suffering from sepsis and one control sample.

The protein expression of one case of sepsis and one control sample were measured. The patients' data are summarized in table 10.

Table 10: Data of the samples of patients and controls

	Gender	Age [a]	Weight/Height	Main diagnosis	Intercurrent diagnosis	Operations	Indication	Apache Score [point]	SAPS II [point]	Selection of clinical data
Control	female	21	62 kg/167 cm	cranio-cerebral-trauma	Generalized cerebral oedema, brain stem contusion, fracture of the lateral orbital pillar, fracture wall left side, lateral fracture of the nasal sceleton, bleeding into the right side ventricle, free air intracraniellfrontally left side, ethmoid bone fracture, fracture of the front pelvic ring with impression and dislocation of the fragments, fracture of the massa lateralis of the OS sacrum right side in the heigh of S1/S2, clavikular fracture left side	none	not applicable	21	-	temperature: 35.3 °c heart rate: 146/min map 1: 68 mmhg; art. ph: 7,48 na: 145 mmol/l; ceratine: 52 µmol/l; syst. bp: 94 mmhg; diast. bp: 56 mmhg; haematocrit: 0,26 % total number of leucocytes: 9200 urea: 7.1 mmol/l; k: 5 mmol/l; bilirubin: 11.1 mmol/l;
Patient	male	59	70 kg/175 cm	septic shock after perforation of one ulcus pylori and subsequent 4 quadrant peritonitis	pleural effusions on both sides, multi organ failure, multiple necrosis of the acra and pretibial on both sides, arterial micro-embolism, arterial thrombosis, secundary thrombocytopenia, acute kidney failure	relaparotomy, lavage, and partial resection of the omentum	septic shock	28	74	temperature: 37.7°c heart rate: 139/min map 1: 64 mmhg; art. ph: 7,15 na: 142 mmol/l, ceratine: 187 mmol/l; breathing rate: 19/min syst. bp: 99 mmhg; diast. bp: 49 mmhg; haematocrit: 24 % hco3: 13.7 mmol/l, total number of leucocytes: 5200 urea: 27.6 mmol/l; pao2!: 13.2 kpa, k: 5.3 mmol/l; bilirubin: 33.9 mmol/l; urine: 110ml, 14h

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Whole blood was drawn and inserted into a serum tube and centrifugation (5500 rcf; 10 min; 4° C) was carried out. The supernatant of serum was transferred into cryo tubes immediately upon centrifugation and stored at -35° C.

To downgrade the albumin, the serum was treated with Affi-Gel Blue Affinity Chromatography Gel for Enzyme and Blood Protein Purifications (Bio-Rad) according to the producer's instructions. To avoid undesired interactions of protein and matrix, the equilibration- and binding buffer were added 400 mM NaCl.

Non-binding proteins were collected and precipitated with methanol and chloroform according to the protocol of Wessel and Flügge (Anal. Biochem. 1984 Apr.; 138(1): 141-3).250 microgram of precipitated serum protein were added to a solution consisting of 8M urea; 2.0 M thiourea; 4% CHAPS; 65 mM DTT and 0.4% (w/v) Bio-Lytes 3/10 (Bio-Rad) and subjected to an isoelectric focusing as well as a subsequent SDS-PAGE.

SDS-PAGE

K4 in figure 1 and in figure 2 is the acute phase protein transthyretin (TTR; P02766, SEQUENCE-ID I.6241, SEQUENCE-ID I.6242) and K5 and K6 are the vitamin D-binding protein (DBP; P02774, SEQUENZ-ID I.1554, SEQUENCE-ID I.1555).

The gels can be produced as follows (Cibacron FT, W1-W3, 400mM NaCl, IEF pH 3-10, Coomassie):

250 microgram of precipitated serum protein were added to a solution consisting of 8M urea; 2.0 M thiourea; 4% CHAPS; 65 mM DTT and 0.4% (w/v) Bio-Lytes 3/10 (Bio-Rad) and subjected to an isoelectric focusing as well as a subsequent SDS-PAGE.

The prepared 2-dimensional gels were colored with Coomassie Brilliant Blau G-250 and differentially expressed proteins were identified by mass spectroscopy.

A comparing analysis shows (figure 1 , figure 2= that the acute phase protein transthyretin (TTR; P02766, SEQUENCE ID: I.6241, SEQUENCE ID I.6242), as well as the vitamin D-binding protein (DBP; P02774, SEQUENCE ID I.1554,

SEQUENCE ID I.1555) are less expressed by the sepsis patient, if compared with the control patient.

These results clearly indicate that the protein expression or the protein composition, respectively, of serum and plasma change in the course of the disease.

Embodiment 5 – Severe Sepsis:

Studies of differential gene expression with patients suffering from severe sepsis.

Whole blood samples of patients who were under the care of a surgical intensive care unit were examined for the measurement of the differential gene expression in connection with severe sepsis.

Control samples were whole blood samples of the patients that were drawn after an uncomplicated neurosurgical operation. The patients were treated on the same intensive care unit. No one of these patients developed an infection and/or showed clinical signs of a generalized inflammatory reaction (defined according to the SIRS-criteria [4]) during the whole time of stationary treatment.

Additionally, whole blood samples were drawn from six male and two female patients (patients' samples). In the time period of 24 hours before the whole blood was drawn, each of these patients developed a new severe sepsis with organ dysfunction. A range of characteristics of the patients suffering from severe sepsis are shown in table 1. Information concerning the age, gender, the cause of the severe sepsis (see diagnosis) as well as concerning the clinical severity, measured with the APACHE-II- and SOFA-Scores (in points each), that are well documented in clinical literature, is given. Equally, the plasma protein levels of procalcitonin (PCT), a new kind of sepsis label, are given, as well as the individual survival conditions.

Table 11: Data of the group of patients

Age	Gender	Diagnosis	Classification according to [4]	Apache II Score [points]	SOFA Score [points]	PCT [ng/ml]	survival conditions
68	female	peritonitis	severe sepsis/	17	4	269	died
39	male	ARDS	septic shock	17	11	0.39	died
36	male	peritonitis	septic shock	11	7	9.77	survived
80	male	peritonitis	severe sepsis	28	4	23.61	survived
32	male	bacterial pancreatitis	septic shock	21	7	1.69	survived
73	male	ARDS	septic shock	16	14	9.96	died
67	male	ARDS	septic shock	24	12	12.88	survived
76	female	peritonitis	septic shock	30	11	4.19	died

After the whole blood had been drawn, the total RNA was isolated using the PAXGene Blood RNS Kit according to the producer's (Qiagen) instructions. Subsequently, the cDNA was synthesized from the total RNA by means of reverse transcription with Superscript II RT (Invitrogen) according to the producer's instructions, labelled with aminoallyl-dUTP and succinimidylester of the fluorescent dyes Cy3 and Cy5 (Amersham), and hydrolyzed.

The microarrays (Lab-Arraytor human 500-1 cDNA) of the company SIRS-Lab GmbH were used for the hybridization. These micorarrays are loaded with 340 human cDNA-molecules. The 340 human cDNA-molecules are 3-fold immobilized in three subarrays on each microarray.

The prepared and labelled samples were hybridized with the microarrays according to the producer's instructions and subsequently washed. The fluorescence signals of the hybridized molecules were measured by means of a scanner (AXON 4000B).

Analysis

One test was analyzed by means of scanned pictures of the microarrays after hybridization. The mean intensity value of the detected spots were defined as the measured expression value of the corresponding gene. Spots were

automatically identified by means of picture analysis and their homogeneity was checked. The analysis was controlled manually. The detected signals comprise not only the desired information, namely the amount of nucleic acids bound, but also background signals which are caused by unspecific bindings to the surface of the membrane. The definition of the signals of the background rendered an optimum differentiation between spots and the surface of the chip possible, which surface also showed color effects. For the analysis of the microarrays blank spots were chosen as background. The mean expression value of the chosen blank spots within one block (of 14 times 14 spots) was subtracted from the expression values of the gene spots (in the corresponding block).

It was possible to distinguish between punctual signals that were caused on the filter by dust particles or other disturbances instead of bindings of nucleic acids, and real spots, due to their irregular form, and the punctual signals were excepted from further analysis.

In order to render the values between the 3 subarrays and between different microarrays comparable, it was necessary to normalize the data afterwards. Due to the high number of spots on the microarray, the mean value of all expression values was set as normalization reference. The mean expression per gene was calculated by choosing the two (from three) repetitions that were closest to each other.

The expression ratios of the samples of the patients and the control were calculated from the signal intensities using the AIDA Array Evaluation software. The criterion for the grading of the examined genes was the level of the expression ratio. The interesting genes were those which were most overexpressed or underexpressed, respectively, compared with the control samples.

Table 12 shows that 41 genes of the patient sample were found, which were significantly overexpressed, if compared with the control sample. Table 13 shows that 89 genes of the patient sample were found, which were significantly underexpressed, if compared with the control sample. Those results show that the genes listed in table 12 and table 13 correlate with the occurrence of a severe sepsis. Furthermore, these results correlate with the clinical classification according to [4] as well as patients' PCT-concentrations, that are typical for the occurrence of a severe sepsis [23]. Thus, the gene activities of the genes mentioned are labels for the diagnosis of a severe sepsis.

Table 12: Expression ratio of overexpressed genes of samples of patients and controls

GenBank Accession No.	HUGO Name	Expression ratio of overexpressed genes compared to control	SEQUENCE-ID
XM_086400	S100A8	4.4	II.1
XM_001682	S100A12	3.03	II.2
NM_002619	PF4	2.21	II.3
NM_002704	PPBP	1.66	II.4
NM_001101	ACTB	1.65	II.5
NM_001013	RPS9	1.61	II.6
XM_057445	SELP	1.61	II.7
BC018761	IGKC	1.53	II.8
XM_030906	TGFB1	1.51	II.9
NM_001760	CCND3	1.48	II.10
XM_035922	IL11	1.28	II.11
XM_039625	DUSP10	1.17	II.12
XM_002762	TNFAIP6	1.17	II.13
XM_015396	ALOX5AP	1.15	II.14
NM_003823	TNFRSF6B	1.15	II.15
XM_029300	DPP4	1.15	II.16
NM_001562	IL18	1.14	II.17
NM_005037	PPARG	1.11	II.18
M90746	FCGR3B	1.07	II.19
NM_001315	MAPK14	0.99	II.20
BC001506	CD59	0.88	II.21
XM_042018	BSG	0.88	II.22
XM_010177	DUSP9	0.87	II.23
BC013992	MAPK3	0.84	II.24
NM_001560	IL13RA1	0.82	II.25
NM_004555	NFATC3	0.74	II.26
NM_001154	ANXA5	0.73	II.27
NM_001310	CREBL2	0.7	II.28
XM_036107	ITGB2	0.65	II.29
XM_009064	JUNB	0.65	II.30
NM_001774	CD37	0.62	II.31
XM_049849	TNFRSF14	0.6	II.32
NM_003327	TNFRSF4	0.57	II.33
BC001374	CD151	0.56	II.34
XM_051958	ALOX5	0.56	II.35
NM_021805	SIGIRR	0.5	II.36
NM_017526	HSOBRGR	0.48	II.37
XM_011780	DAPK1	0.46	II.38
NM_006017	PROML1	0.44	II.39
D49410	IL3RA	0.43	II.130
XM_027885	RPL13A	0.33	II.40

Table 13: Expression ratio of underexpressed genes of samples of patients and controls

GenBank Accession No.	HUGO Name	Expression ratio of underexpressed genes compared to control	SEQUENCE-ID
NM_007289	MME	-2.11	II.41
XM_008411	SCYA13	-2.06	II.42
XM_055188	ENG	-2.01	II.43
NM_021073	BMP5	-1.99	II.44
XM_007417	TGFB3	-1.93	II.45
NM_001495	GFRA2	-1.88	II.46
XM_009475	AHCY	-1.86	II.47
XM_006738	CD36L1	-1.86	II.48
NM_001772	CD33	-1.86	II.49
NM_057158	DUSP4	-1.83	II.50
XM_058179	CD244	-1.77	II.51
NM_001770	CD19	-1.75	II.52
NM_004931	CD8B1	-1.73	II.53
XM_006454	CD3G	-1.71	II.54
XM_041847	TNF	-1.65	II.55
NM_145319	MAP3K6	-1.62	II.56
XM_045985	ITGA2B	-1.61	II.57
XM_055756	TIMP1	-1.61	II.58
NM_004740	TIAF1	-1.61	II.59
XM_008432	ITGA3	-1.57	II.60
XM_034770	PAFAH1B1	-1.56	II.61
NM_014326	DAPK2	-1.55	II.62
XM_043864	PIK3R1	-1.49	II.63
U54994	CCR5	-1.49	II.64
NM_004089	DSIPI	-1.49	II.65
XM_037260	F2R	-1.45	II.66
NM_172217	IL16	-1.45	II.67
AF244129	LY9	-1.45	II.68
NM_003775	EDG6	-1.43	II.69
NM_001781	CD69	-1.41	II.70
NM_019846	CCL28	-1.39	II.71
NM_001511	CXCL1	-1.38	II.72
NM_006505	PVR	-1.33	II.73
NM_000075	CDK4	-1.33	II.74
XM_042066	MAP3K1	-1.32	II.75
NM_003242	TGFBR2	-1.31	II.76
NM_003874	CD84	-1.31	II.77
XM_033972	ATF6	-1.3	II.78
XM_001840	PLA2G2A	-1.3	II.79
NM_018310	BRF2	-1.29	II.80
AF212365	IL17BR	-1.25	II.81
XM_056798	CD81	-1.25	II.82
NM_000061	BTK	-1.24	II.83
XM_001472	JUN	-1.23	II.84
XM_007258	TNFAIP2	-1.23	II.85
XM_048555	IFNAR2	-1.23	II.86

GenBank Accession No.	HUGO Name	Expression ratio of underexpressed genes compared to control	SEQUENCE-ID
XM_041060	FOS	-1.23	II.87
XM_056556	TNFSF7	-1.23	II.88
XM_016747	LTBP1	-1.22	II.89
XM_006953	TNFRSF7	-1.21	II.90
NM_015927	TGFB1I1	-1.19	II.91
XM_010807	INHBB	-1.16	II.92
NM_002184	IL6ST	-1.14	II.93
XM_008570	VAMP2	-1.13	II.94
NM_006856	ATF7	-1.1	II.95
NM_000674	ADORA1	-1.09	II.96
NM_000173	GP1BA	-1.08	II.97
XM_048068	SCYD1	-1.07	II.98
NM_022162	CARD15	-1.07	II.99
NM_001199	BMP1	-1.02	II.100
NM_000960	PTGIR	-1.01	II.101
XM_012039	FUT4	-0.99	II.102
XM_034166	NOS2A	-0.99	II.103
NM_003188	MAP3K7	-0.98	II.104
NM_006609	MAP3K2	-0.98	II.105
XM_027358	PCMT1	-0.95	II.106
XM_007189	FOXO1A	-0.93	II.107
XM_030523	MAP3K8	-0.92	II.108
XM_002923	CCR2	-0.88	II.109
XM_054837	TNFRSF1B	-0.87	II.110
NM_000634	IL8RA	-0.87	II.111
NM_004590	CCL16	-0.86	II.112
XM_012717	CSNK1D	-0.86	II.113
XM_012649	SCYA7	-0.84	II.114
XM_008679	TP53	-0.84	II.115
XM_030509	PTGIS	-0.83	II.116
XM_039086	CDW52	-0.82	II.117
XM_027978	CFLAR	-0.81	II.118
NM_005343	HRAS	-0.79	II.119
XM_043574	DAP3	-0.78	II.120
NM_002188	IL13	-0.77	II.121
XM_055699	ENTPD1	-0.72	II.122
NM_000565	IL6RA	-0.67	II.123
NM_002211	ITGB1	-0.65	II.124
XM_049864	CSF3	-0.63	II.125
XM_045933	CAMKK2	-0.63	II.126
NM_033357	CASP8	-0.55	II.127
XM_008704	DNAM-1	-0.52	II.128
NM_030751	TCF8	-0.5	II.129

It is for example possible to take advantage of these characteristic changes in the method of the present invention according to claim 3 and 32.

In the appended sequence listing of 1430 pages, which is part of the present invention, the gene bank accession numbers (access via internet via http://www.ncbi.nlm.nih.gov/) indicated in tables 12 and 13 of the individual sequences are each allocated to one sequence ID. (SEQUENCE ID No.: II.1 to SEQUECE ID No. II.130). The following sequence listing is part of the present invention.

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